# Novel Therapies For Chronic Urticaria and Angioedema

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# Relevant Disclosures

- Research Investigator
  - Genentech
  - Novartis
  - Merck
  - Circassia
  - Cytos
- Consultant
  - Stallergenes
  - Novartis
  - Genentech
  - Circassia
  - Cytos
  - Teva

# Objectives

- Discuss the shortfalls of current therapies for chronic urticaria
- Explain the rationale behind new therapies for chronic urticaria

# Management Of Chronic Urticaria

**Step 1**
- Avoidance of triggers
- Monotherapy with second generation antihistamine

**Step 2**
- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add $H_2$- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine (at bedtime)

**Step 3**
- Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

**Step 4**
- Anti-inflammatory agent
- Immunosuppressant
- Biologics

Urticaria Practice Parameter Update

# Antihistamine Refractory Urticaria/Angioedema Treatment Options

- Colchicine
- Sulfasalazine
- Mycophenolate
- Methotrexate
- Dapsone
- Sirolimus
- Anti-TNF
- Stanozolol
- IVIG
- Stanozolol
- Hydroxychloroquine
- Omalizumab
- Cyclosporine
- Others…

# Anti-inflammatory Agents

- Dapsone
  - Suppression of PG and LT activity
  - Anti-neutrophil activity
  - Check for G6PD deficiency and monitor Hb and LFTs
- Sulfasalazine
  - Decreased PGD2 synthesis and histamine release from activated mast cells
  - GI symptoms
- Hydroxychloroquine
  - Disrupts T-cell receptor crosslinking-dependent Ca signaling
  - Monitor for retinopathy
- Colchicine
  - Anti-neutrophil activity
  - Diarrhea

# Immunosuppressant Agents

- Calcineurin Inhibitors: **Cyclosporine** & Tacrolimus

- Mycophenolate mofetil (MMF)
  - Competitive inhibitor of IMP dehydrogenase
  - Kills activated lymphocytes through caspase-independent necrotic signal
  - GI side effects
  - Works in 1 to 9 weeks

- Sirolimus (rapamycin): prevents activation of T and B cells by inhibiting their response to IL-2

- Cyclophosphamide

- Methotrexate

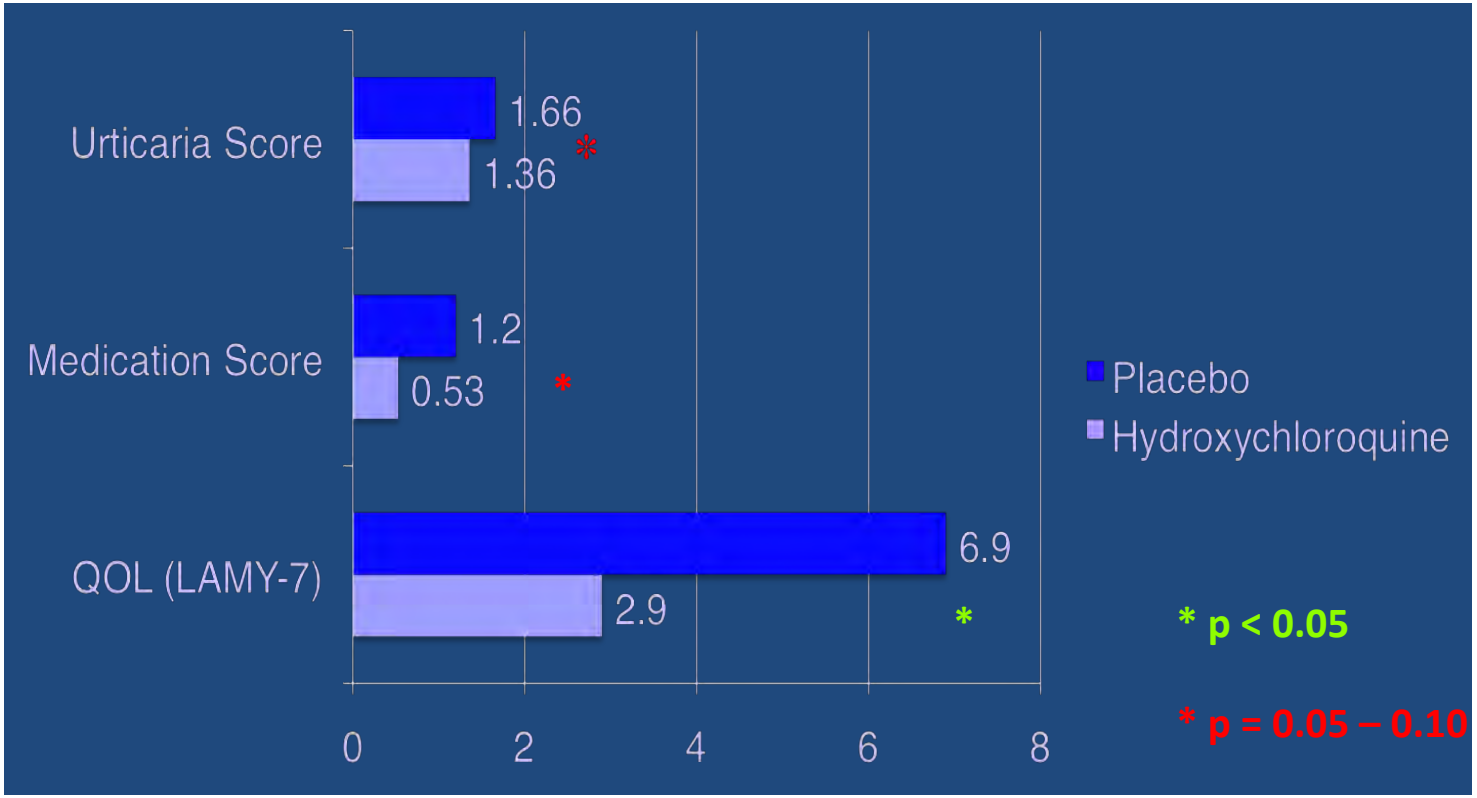
# Evaluating Therapeutic Utility of Alternative Agents for Refractory CU/Angioedema

- Case Series and Case Reports are subject to bias, and do not provide high quality evidence.

- Only three agents have been studies in randomized controlled trials:
  - Hydroxychloroquine
  - Cyclosporine
  - Omalizumab
    - Preferred biologic agent for refractory CU

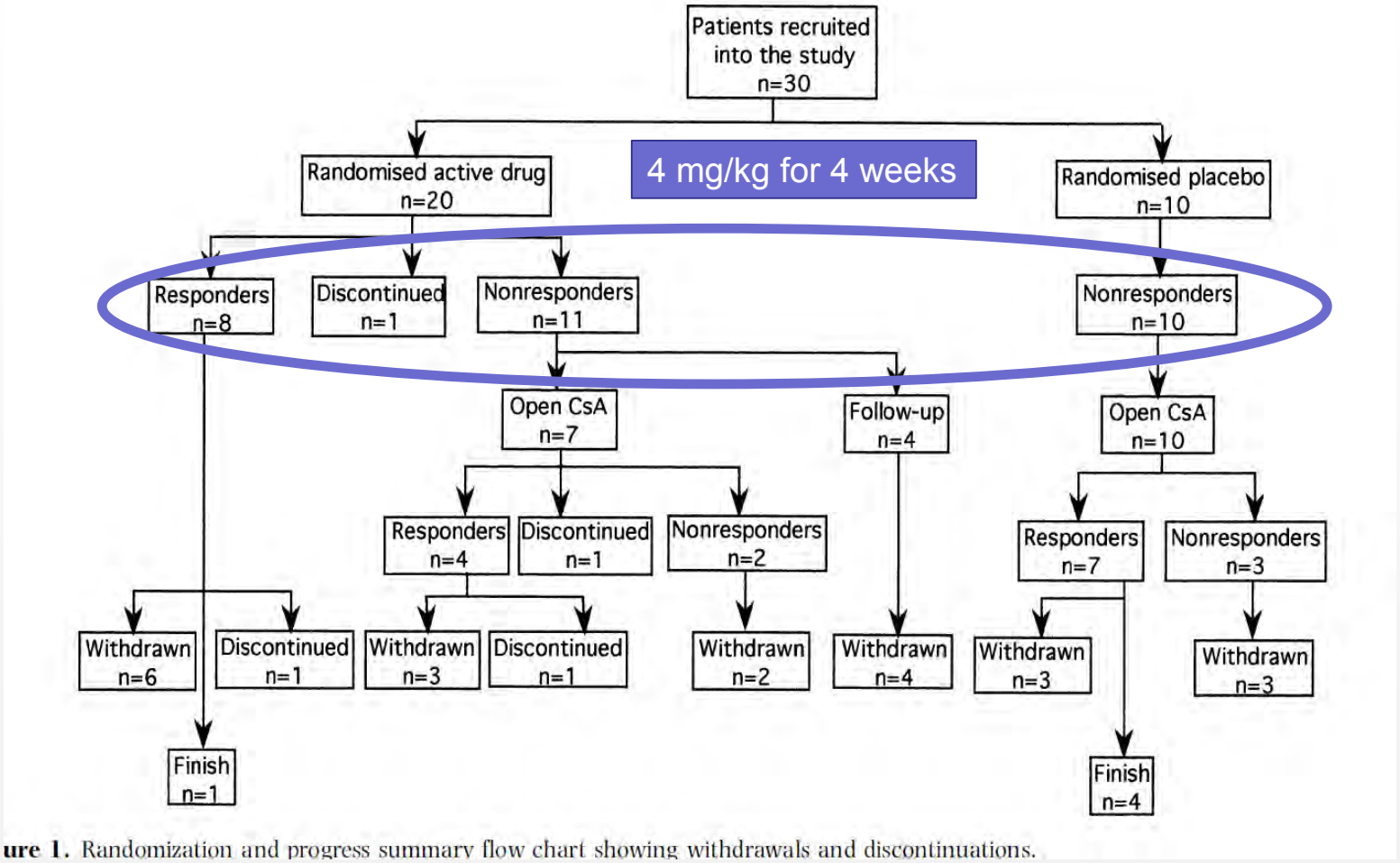
# RCT: Hydroxychloroquine

- 21 patients with chronic urticaria/angioedema, randomized to Hydroxychloroquine or placebo for 12 weeks, in addition to other medications for urticaria (H1 & H2 antihistamines, doxepin, corticosteroids).
- Med taper q 2 weeks if well controlled; 18 completed trial, ITT analysis.




*Reeves GEM, et al. Intern Med J 2004; 34: 182-6.*

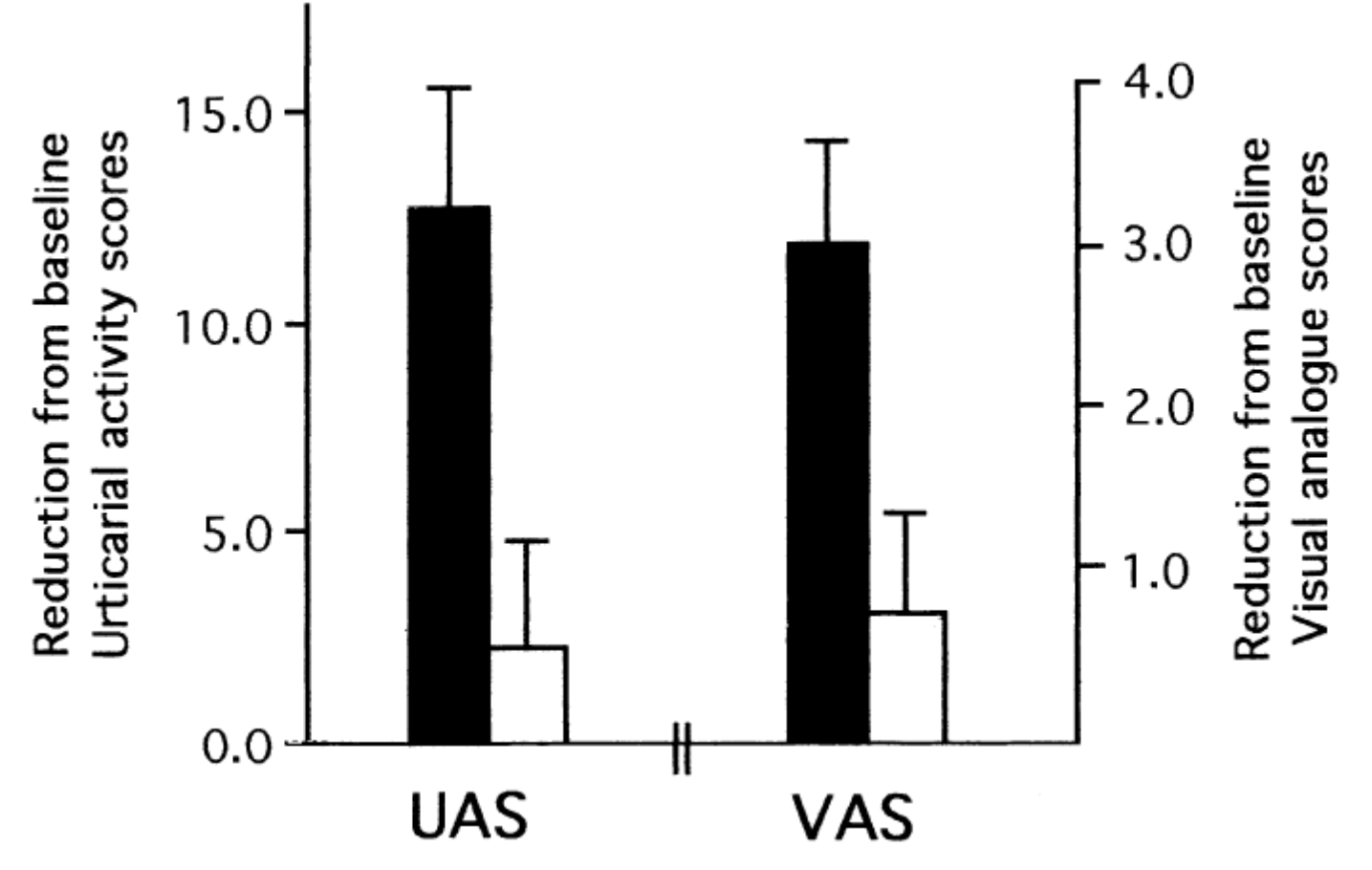
# Study Flow Chart For Cyclosporine Trial




ure 1. Randomization and progress summary flow chart showing withdrawals and discontinuations.

Grattan et al, BJD, 2000

# Cyclosporine Response at 4 Weeks




Grattan et al, BJD, 2000

# Cyclosporine

- It is unclear whether the potential for desirable effects significantly outweighs the risk for undesirable effects, particularly with the lack of an appropriate comparator group (e.g., cetirizine 10-20 mg/day) enrolled in these studies.

- In the context of study limitations, potential harms and costs, the quality of evidence supporting cyclosporine administration is LOW -- leading to a WEAK RECOMMENDATION, based on current evidence.

- This recommendation implies that future research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

•*Bernstein J, et al.* **The Diagnosis and Management of Acute and Chronic Urticaria: 2013 Update. Submitted**

# First of 3 DBRCT with Omalizumab

The NEW ENGLAND JOURNAL of MEDICINE

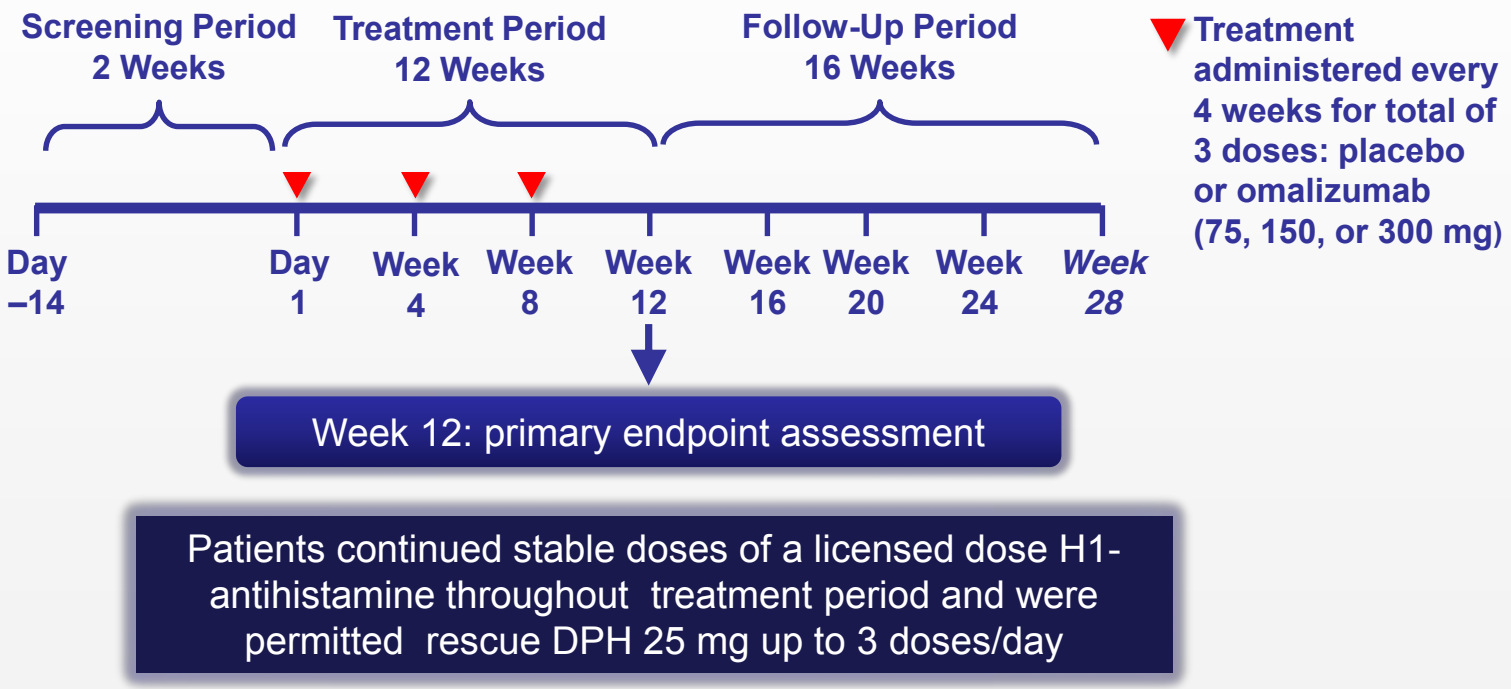
ORIGINAL ARTICLE

## Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

Marcus Maurer, M.D., Karin Rosén, M.D., Ph.D., Hsin-Ju Hsieh, Ph.D., Sarbjit Saini, M.D., Clive Grattan, M.D., Ana Gimenéz-Arnau, M.D., Ph.D., Sunil Agarwal, M.D., Ramona Doyle, M.D., Janice Canvin, M.D., Allen Kaplan, M.D., and Thomas Casale, M.D.

March 2013

# Study Design – Asteria II




DPH=diphenhydramine

# Primary Endpoint: Change From Baseline In Weekly Itch-Severity Score At Week 12 (mITT)

- Significant improvements in weekly ISS with omalizumab 150 mg and 300 mg doses vs. placebo

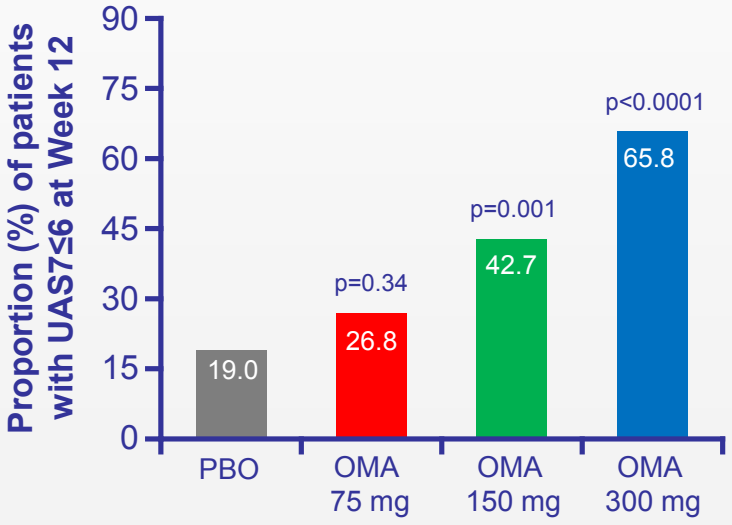
| Change from baseline in weekly ISS at Week 12 | Placebo (N=79) | Omalizumab 75 mg (N=82) | Omalizumab 150 mg (N=82) | Omalizumab 300 mg (N=79) |
|---|---|---|---|---|
| Mean (SD) | –5.1 (5.6) | –5.9 (6.5) | –8.1 (6.4) | –9.8 (6.0) |
| LSM treatment difference vs. placebo (95% CI) | | –0.7 (–2.5, 1.2) | **–3.0 (–4.9, –1.2)** | **–4.8 (–6.5, –3.1)** |
| p value | | 0.4637 | **0.0011** | **<0.0001** |

CI=confidence interval; ISS=Itch-Severity Score; LSM=least squares mean; mITT=modified intention-to-treat population; SD=standard deviation

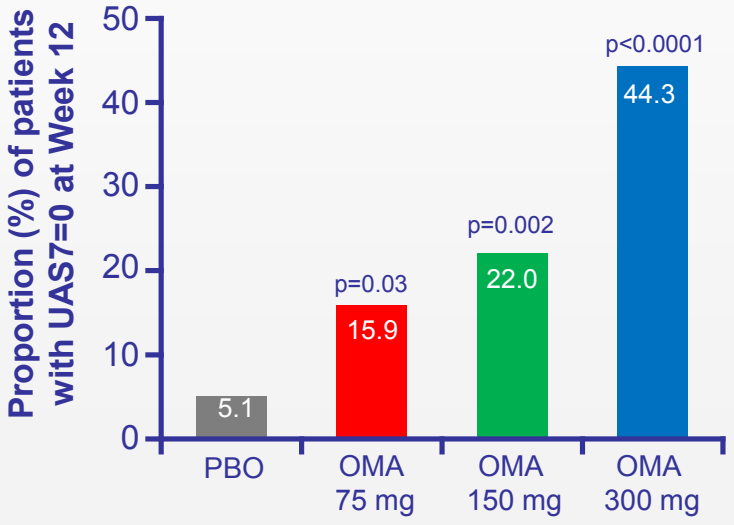
# Responder Analysis (mITT)

- **Significantly higher proportion of patients in omalizumab 150 mg and 300 mg groups had symptoms which were well controlled (UAS7≤6) vs. placebo**
- **A large proportion of patients treated with omalizumab 300 mg were completely symptom free (UAS7=0) by Week 12**

**UAS7≤6 (secondary endpoint)**




**UAS7=0 (post-hoc analysis)**




mITT=modified intention-to-treat population; OMA=omalizumab; PBO=placebo; UAS7=weekly urticaria activity score

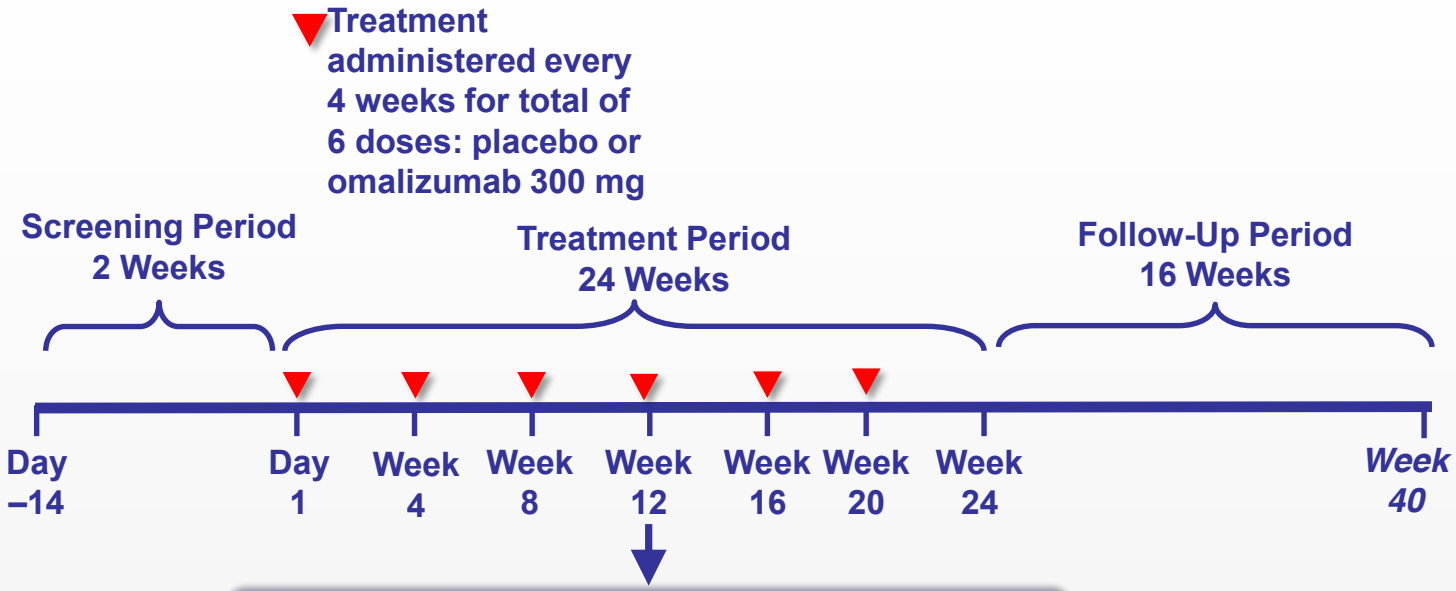
# Omalizumab in Guideline-Driven Care

## Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy

Allen Kaplan, MD,[a] Dennis Ledford, MD,[b] Mark Ashby, PhD,[c] Janice Canvin, MD, FRCPC,[d] James L. Zazzali, PhD,[c] Edward Conner, MD,[c] Joachim Veith, MD,[c] Nikhil Kamath, MD,[e] Petra Staubach, MD,[f] Thilo Jakob, MD,[g] Robert G. Stirling, MB, FRACP,[h] Piotr Kuna, MD, PhD,[i] William Berger, MD,[j] Marcus Maurer, MD,[k] and Karin Rosén, MD, PhD[c] *Charleston, SC, Tampa, Fla, South San Francisco and Mission Viejo, Calif, Horsham and Welwyn Garden City, United Kingdom, Mainz, Freiburg, and Berlin, Germany, Melbourne, Australia, and Lodz, Poland*

JACI, July 2013

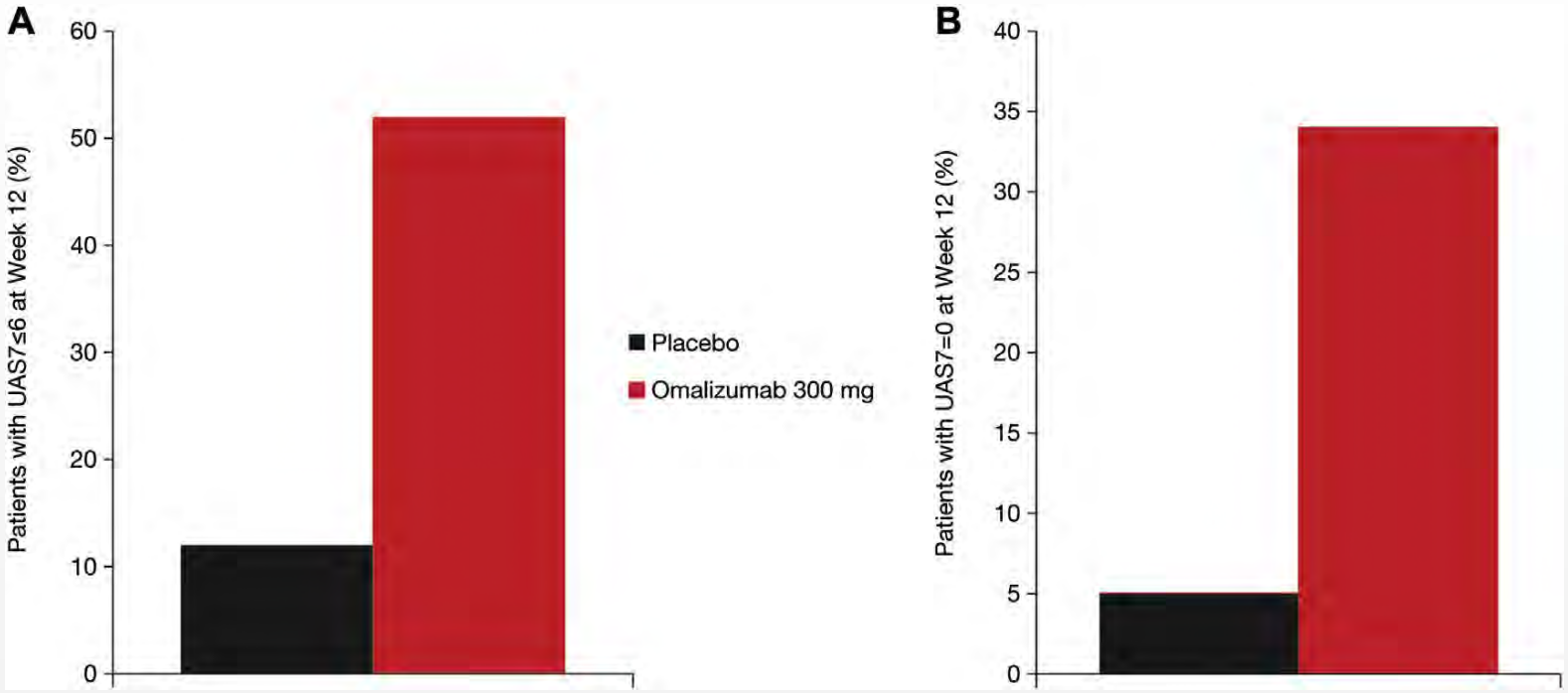
# Study Design



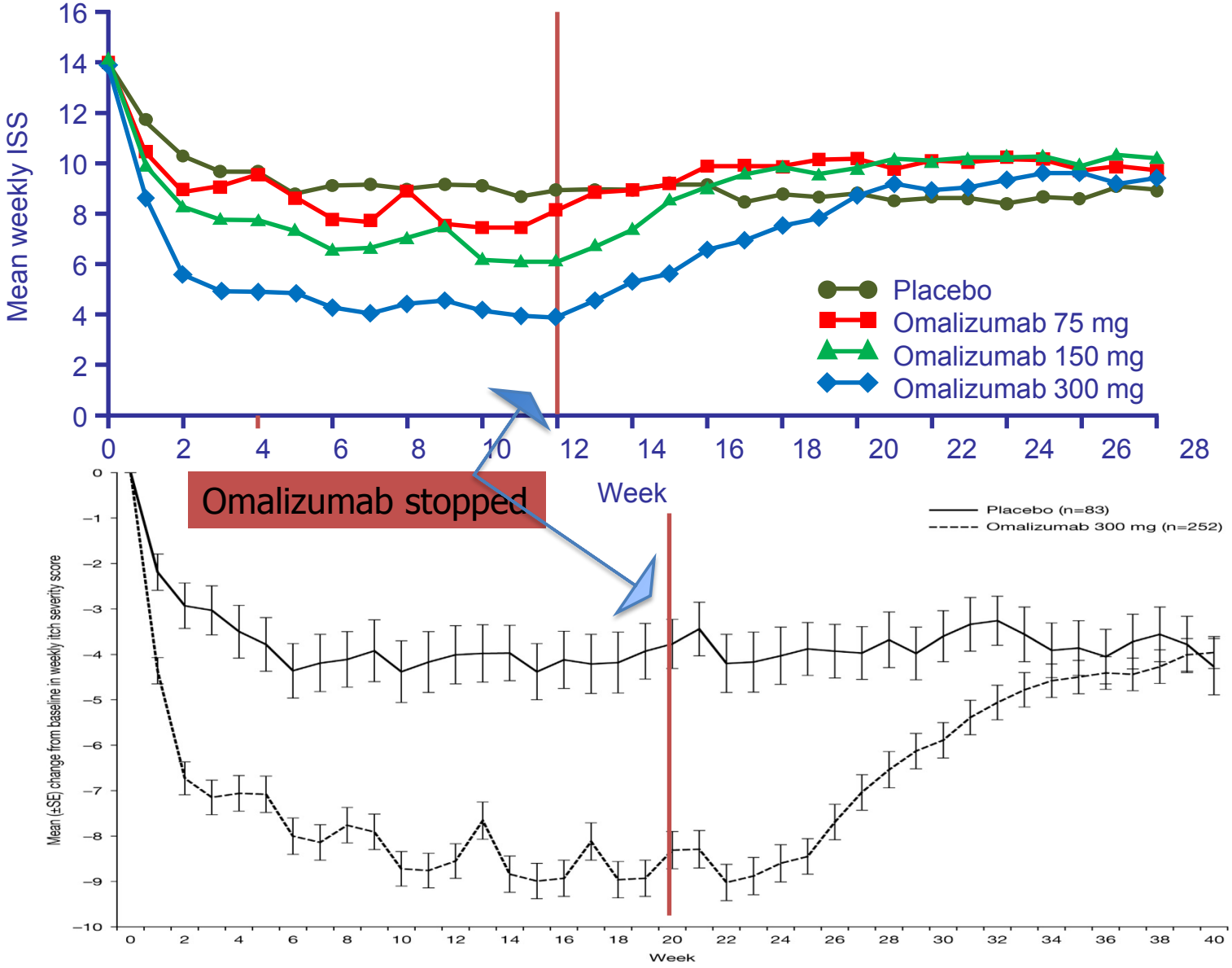

Patients continued stable doses of H1-antihistamines, H2 antihistamines and/or LTRA throughout treatment period and were permitted rescue DPH 25 mg up to 3 doses/day

DPH=diphenhydramine

# Omalizumab Responder Analysis



# Omalizumab Duration of Action



# Algorithm For Antihistamine Refractory CU
## Non-Evidence Based

**Step 1**
- Continue high dose 2nd generation H1-blockers
- Eliminate triggers

**Step 2**
- Consider biopsy
- If neutrophilic, trial of dapsone or colchicine

**Step 3**
- Omalizumab 150 mg/month
  - If partial (or no) response increase to 300 mg/month
  - If no response, consider cyclosporine

**Step 4**
- Use whatever works with the best safety profile and least cost

# CU Summary and Conclusions

- Antihistamines, the mainstay of therapy, are ineffective in as many as 50% of CU patients.
- Systemic corticosteroids, although effective in many patients, have predictable systemic toxicities especially with chronic use.
- A number of therapeutic alternatives have been evaluated to treat antihistamine-refractory CU in order to reduce the need for systemic corticosteroids.
- Limited evidence for many alternative therapies in antihistamine refractory CIU patients and some require monitoring for adverse effects
  - Omalizumab data support placement in therapy of anti-histamine-resistant CU